REMARKS

I. Introduction

In response to the Office Action dated April 2, 2009, claims 1 and 16 have been amended. Claims 1-18 remain in the application. Reconsideration of the application, as amended, is requested.

II. Claim Amendments

Applicants' attorney has made amendments to the claims as indicated above. These amendments were made solely for the purpose of clarifying the language of the claims, and do not introduce new matter. Support for the amendments can be found in the application as originally filed as follows.

Support for the amendment to claims 1 and 16 can be found in the specification at page 4, lines 12-14, and at page 10, line 4. Support for the recited deuterated materials can be found at page 5, lines 14 and 20, and at page 11, line 12.

III. Restriction Requirement

Applicants appreciate the indication, at page 2 of the Office Action, that the requirement for restriction was withdrawn.

IV. Non-Art Rejections

A. Enablement

At pages 3-6 of the Office Action, claims 1-18 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not supported by an enabling disclosure commensurate with the scope of the claims. More specifically, the specification is regarded as enabling for a method comprising introducing living cells into a container loaded with D2O and using measurement of Raman spectra, but not for use with "any deuterated materials" and "obtaining vibrational spectra".

Reconsideration and withdrawal of this rejection is respectfully requested, particularly in view of the amendments to the claims. As amended, independent claims 1 and 16 clarify that the "deuterated materials" are those described in the specification, namely, deuterated water, glucose and/or amino acids. Likewise, the "vibrational spectra" are clarified to be those

described in the specification, namely, Raman, resonance Raman, infrared (IR) and/or near infrared (NIR).

Applicants respectfully disagree with the assertion at page 6 of the Office Action that "Applicant provides no particular guidance in the instant specification regarding a method of providing deuterated materials other than D2O and does not provide any working examples or guidance with regard to practicing a method of obtaining a vibrational spectra emitted by living cells and associating such spectra with metabolism so as to provide an indication of viability of the cells". The specification does in fact provide such guidance, for example, at page 5, wherein it provides examples for using glucose as the deuterated agent, including listing a number of specific examples of deuterated forms of glucose. Pages 6-9 of the specification provide extensive guidance for various methods of using normalization to facilitate identification of spectral information associated with the analyte(s) of interest that will provide information indicative of cell viability, including guidance on using spectra detectable in the near infrared range (see page 9, first full paragraph).

Applicants respectfully note that those skilled in the art are well aware of the ability to detect vibrational spectra of a variety of analytes in the near infrared and infrared range. One example of knowledge in the art regarding use of near infrared spectroscopy to measure metabolically relevant analytes, such as glucose, is Rhiel et al., 2002, "Nondestructive Near-Infrared Spectroscopic Measurement of Multiple Analytes in Undiluted Samples of Serum-Based Cell Culture Media", *Biotechnology & Bioengineering* 77: 73-82 (glucose, lactate, glutamin, ammonia), a copy of which is submitted herewith as Exhibit A. An example of knowledge in the art of using Raman spectroscopy to monitor analytes other than D2O is Chaiken et al., 2001, "Noninvasive blood analysis by tissue modulated NIR Raman spectroscopy", *SPIE* 4368: 134-145, a copy of which is submitted herewith as Exhibit B. Chaiken et al. show the ability to track blood glucose concentration using Raman spectroscopy with a very high correlation to conventional fingerstick measurements of blood glucose (see Figure 5).

The claimed invention addresses the need for an improved process to determine cell viability by making use of deuterated materials to measure absolute and relative rates of metabolic activity and/or integrity of the cell membrane with vibrational spectroscopy (see specification, page 1, line 19, to page 2, line 6). The working examples provided at pages 10-12 of the specification detail the claimed method as performed with D2O and Raman spectroscopy. In addition, guidance is provided for substituting other deuterated materials for

D20 and the specification suggests various target wavenumbers, as well as other reference wavenumbers, at pages 2 and 5-9.

Moreover, one skilled in the art can readily adapt the teachings of the specific embodiments described in the working examples to other embodiments encompassed by the claims using information that was well known in the art at the time the application was filed. The skilled person would know how to substitute the deuterated reagent for the protonated version in a conventional or commercial growth medium. Applicant's teaching to choose a deuterated glucose (or amino acid) is sufficient to instruct those skilled in the art how to practice the claimed method without requiring undue experimentation. Likewise, the skilled person would know how to adapt known methods of using vibrational spectroscopy to probe the deuterated materials. The Holman et al. article cited in the Office Action is an example of knowledge in the art of how to use IR spectroscopy to detect changes in spectral regions corresponding to proteins (amino acids). The Rhiel et al. article of Exhibit A is an example of the ability of skilled persons to probe analytes using NIR. The Holtom et al. article cited in the Office Action is an example of knowledge in the art regarding vibrational spectroscopic detection of deuterated compounds.

The level of predictability in the art is one of the *Wands* factors to be considered in the evaluation of compliance with the enablement requirement, as acknowledged in the Office Action. The Office Action does not, however, provide any technical reasoning or even an unsupported assertion that the nature of the relevant art is so unpredictable as to require undue experimentation in order to apply the teachings of Applicants' specification to use vibrational spectra indicative of metabolism as a means to determine viability of living cells in culture by placing the cultured cells into a container loaded with deuterated materials. The detailed embodiment exemplified at pages 10-12 of the specification, using D2O and Raman spectroscopy, is more than adequate to provide the skilled person with a reasonable expectation of success when substituting deuterated glucose or amino acids for D2O, and/or substituting IR or NIR for Raman spectroscopy.

Accordingly, Applicants respectfully request withdrawal of the rejection based on the enablement requirement.

B. Indefiniteness

At page 7 of the Office Action, claims 1-3 and 6-18 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Applicants have amended independent claims 1 and 16 to clarify the language noted in the Office Action. Specifically, the claims have been amended to clarify that "deuterated materials are selected from the group consisting of water, glucose and an amino acid", and that "vibrational spectra are selected from the group consisting of Raman, infrared and near infrared spectra".

Reconsideration and withdrawal of the rejection for indefiniteness is respectfully requested.

V. Office Action Prior Art Rejections

At pages 7-8 of the Office Action, claims 1-3 and 6-18 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Chaiken et al. (US 6,503,478). Applicants respectfully traverse this rejection.

US Patent No. 6,503,478 teaches methods for obtaining spatially resolved images of specific types of tissues by applying a deuterated imaging agent to the tissue and performing spectroscopy. This allows one to map out a specific volume of tissue, obtaining information regarding the distribution of specific endogenous chemical species (see Abstract). This method involves determining a surface fractal dimension of a portion of the tissue, typically skin (cols. 2-3 and 6), and is based on the discovery that deuterated imaging agents can be used to obtain distinct spectroscopic signals from deep as well as superficial portions of living tissue (col. 4, l. 3-6).

The claimed invention, as set forth in independent claim 1, is directed to a method of determining viability of living cells, comprising 3 steps. The first step is obtaining a container loaded with deuterated materials. The second step is introducing a sample of cultured living cells into the container whereby the living cells are in contact with the deuterated materials. The third step is obtaining vibrational spectra emitted by the living cells. The vibrational spectra emitted by the living cells are indicative of metabolism, thereby providing an indication of viability of the cells, such that greater metabolic activity is indicative of greater viability.

The cited reference fails to teach all elements of Applicants' claims, including independent claim 1. The Office Action fails to address each element of Applicants' independent claims, and fails to address all elements of each of the dependent claims.

In particular, the cited reference does not teach a method of determining viability of living cells, and it does not teach the first two steps of claim 1, nor does it teach obtaining vibrational spectra emitted by living cells that are indicative of metabolism as a measure of viability. For example, the cited reference teaches placing a specifically-binding molecule that has been modified to contain a deuterium substitution into contact with the tissue to be imaged by spreading or spraying the molecule onto the target tissue (col. 7, l. 52-60).

Because the cited reference is directed to imaging skin, e.g., in vivo, it does not contemplate, teach or suggest introducing a sample of living cells into a container loaded with deuterated materials to bring the living cells into contact with the deuterated materials. To further clarify the distinction between the claimed method and that of the cited reference, Applicants have amended claim 1 to clarify that the living cells to be introduced into the container are cultured cells.

Independent claim 16 is further removed from the teachings of the cited reference, as it recites additional steps wherein an aliquot of the cells are placed into a medium free of deuterated materials and determining the rate of decrease of emitted vibrational spectra, whereby a faster rate of decrease of emitted vibrational spectra after placement in the medium free of deuterated materials is indicative of greater viability.

As with claim 16, the Office Action fails to point out how the cited reference anticipates each element of the dependent claims included in the rejection. For example, the cited reference makes no mention or suggestion of normalizing the Raman spectra obtained by comparing the Raman spectra obtained at a target wavelength to the fluorescence generated by a Raman excitation source, as recited in dependent claim 13, nor does it contain any teaching or suggestion to use a centrifuge tube as the container loaded with deuterated materials as recited in dependent claim 15. Likewise, the limitations recited in dependent claims 17 and 18 are even farther removed from the teachings of the cited reference.

Because the reference cited in the Office Action fails to teach each element of Applicants' claims, the rejection based on the prior art is in error and should be withdrawn.

VI. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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Date: 31 July 2009